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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/229,283	01/13/1999	DAVID E. FISCHER	48012	7211

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	12

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/229,283	Fischer
Examiner	**Art Unit**
Ungar	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 22, 2000* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above, claim(s) *5-12* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The Election filed February 22, 2000 (Paper No. 9) in response to the Office Action of January 18, 2000 (Paper No. 7) is acknowledged and has been entered. Claims 1-12 are pending in the application and Claims 5-12 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-4 are currently under prosecution.

2. Applicant's election with traverse of Group I, claims 1-4 in Paper No 9 is acknowledged. The traversal is on the ground(s) that Groups I and II fall into the same search group and therefore the search of Group I is coextensive with Group II, that is, the examination of both of these groups would not impose a serious burden on the examiner. This is not found persuasive because classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and because different searches and issues are involved in the examination of each group. Further Applicant notes that Examiner never discussed any difference between Groups I and II but rather contrasted them with Groups III and IV. Examiner appreciates Applicant pointing out the inadvertent typographical error in the restriction requirement section dealing with distinct methods. Since both Group I and Group II are clearly enumerated as methods and Group III is clearly a product claim and Group III is listed not only in the distinct method section but also in the distinct product section, it is clear that it was a typographical error, rather than an improper restriction requirement that is disclosed. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Further, applicant elects the species of antibody, claim 2 for examination. . Because applicant did not distinctly and specifically point out the supposed errors in the species election requirement, the election has been treated as an election without traverse (MPEP 818.03(a).

3. It is noted that item AG was crossed out on submitted form 1449. Although the report was considered, it is not possible to include it in the IDS because it is not a publication.

Oath/Declaration

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because:

(a) Inventor Fischer's Zip code has been altered, but the alteration has not been initialed and dated.

Specification

5. The specification on page 1 should be amended to reflect the status of the parent application serial number 60/071,420. The following format is suggested,

"This application claims benefit to provision application 60/071,420, filed January 14, 1998, now abandoned."

6. The use of the trademarks such as "Puregene" disclosed on page 18, line 2 of the specification has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Each letter of the trademarks must be capitalized. See MPEP 608.01(V) and Appendix I. Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where else they may be found. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

8. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing melanoma which comprises contacting, *in vitro*, a biological specimen of malignant cells with a probe which selectively recognizes microphthalmia (Mi) wherein the biological specimen does not include melanocytes, mast cells or osteoclasts, does not reasonably provide enablement for a method for diagnosing melanoma which comprises contacting a biological specimen with a probe which selectively recognizes microphthalmia. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for diagnosing melanoma comprising contacting a biological specimen with a probe which selectively recognizes Mi and determining whether Mi is expressed in the specimen by probe's binding to Mi, wherein said binding is indicative of Mi expression and wherein the expression of Mi in a malignant cell is indicative of melanoma. The claims as written are drawn to contacting any biological specimen *in vivo* and/or *in vitro*.

The specification teaches that determining the origin of a metastatic tissue arising from a melanoma is extremely difficult (p. 2, lines 8-9). The ability to determine the origin of a metastatic disease is very important because it can affect the diagnosis and/or type of treatment regime prescribed and a more accurate means for diagnosing melanoma is important (p. 2, lines 13-18). Microphthalmia (Mi/MITF) is a transcription factor implicated in pigmentation, mast cells and bone development (p. 5, lines 19-21). The inventors have discovered that there is a high correlation between the presence of Mi in a malignant cell, that cell being melanoma (p. 6, lines 29-31). Mi is a sensitive and specific marker for melanoma. Antibody to Mi was shown to strongly stain the nucleus of melanocytes, nevi, dysplastic nevi, melanoma in situ, and 100% of 76 consecutively acquisitioned melanomas, including amelanotic and metastatic tumors (para bridging pages 10-11). Since Mi is normally present in melanocytes, mast cella and osteoclasts, biological specimen preferably does not include those cells (p. 8, lines 25-27). The specification teaches monoclonal antibody D5, raised against a histidine fusion protein expressed from

the amino terminal Taq-Sac fragment of human MITF cDNA of Tachibana et al (Hum. Mol. Genet., 1994, 3:553-7557, cited in the specification) which is specific for Mi, but not related proteins (p. 14, lines 25-30). Further, polyclonal antibodies to the same His fusion appear to have been generated and have been shown to not be cross reactive on DNA mobility shift assays (para bridging pages 16-17) with other proteins. Histopathology on human melanoma tissue was performed using antibody D5 to Mi (p. 20, lines 10-15).

One cannot extrapolate the teaching of the specification to the scope of the claims because it is not clear how one would diagnose melanoma or, for example, differentiate a malignant cell from a normal melanocyte or non-malignant cell based only on the binding of an antibody to microphthalmia because the specification clearly teaches that antibody D5 heavily stains the nucleus of not only melanoma cells and melanoma *in situ*, but also heavily stains the nucleus of melanocytes, nevi and dysplastic nevi as well as normal skin as shown in Figure 6. Further, the specification specifically teaches that since Mi is normally present in melanocytes, mast cells and osteoclasts and suggests that the biological specimen preferably does not include those cells. Clearly the concern here is for artifacts that would result in false positive findings leading to misdiagnosis and incorrect institution of treatment protocols. For the same reasons, it could not be predicted, nor would it be expected that one could successfully diagnose melanoma in the *in vivo* environment, given the variety of cell types which would be expected to be identified with an antibody probe. In the absence of further guidance and in view of the similarity of staining in multiple tissue types disclosed in the specification, one of skill in the art would be

forced into undue experimentation to practice the claimed invention. The rejection may be obviated by amending claim 1, for example, to read contacting an *in vitro* biological specimen of malignant cells with a probe.

9. If applicant were able to overcome the rejection set forth above, claims 1-4 would still be rejected under 35 USC 112, first paragraph because the specification, while being enabling for a method for diagnosing melanoma which comprises contacting a biological specimen with a probe which selectively recognizes the amino terminal Taq-Sac fragment of human MITF cDNA of Tachibana et al or the polynucleotide of Tachibana et al encoding said fragment, does not reasonably provide enablement for a method for diagnosing melanoma which comprises contacting a biological specimen with a probe which selectively recognizes microphthalmia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for diagnosing melanoma comprising contacting a biological specimen with a probe which selectively recognizes Mi and determining whether Mi is expressed in the specimen by probe's binding to Mi, wherein said binding is indicative of Mi expression and wherein the expression of Mi in a malignant cell is indicative of melanoma. This includes a probe that selectively recognizes any microphthalmia isoform.

The specification teaches that determining the origin of a metastatic tissue arising from a melanoma is extremely difficult (p. 2, lines 8-9). The ability to determine the origin of a metastatic disease is very important because it can affect

the diagnosis and/or type of treatment regime prescribed and a more accurate means for diagnosing melanoma is important (p. 2, lines 13-18). Microphthalmia (Mi/MITF) is a transcription factor implicated in pigmentation, mast cells and bone development (p. 5, lines 19-21). The inventors have discovered that there is a high correlation between the presence of Mi in a malignant cell and that cell being melanoma (p. 6, lines 29-31). Mi is a sensitive and specific marker for melanoma. Antibody to Mi it was shown to strongly stain the nucleus of melanocytes, nevi, dysplastic nevi, melanoma in situ, and 100% of 76 consecutively acquisitioned melanomas, including amelanotic and metastatic tumors (para bridging pages 10-11). Since Mi is normally present in melanocytes, mast cella and osteoclasts, biological specimen preferably does not include those cells (p. 8, lines 25-27). The specification teaches monoclonal antibody D5, raised against a histidine fusion protein expressed from the amino terminal Taq-Sac fragment of human MITF cDNA of Tachibana et al (Hum. Mol. Genet., 1994, 3:553-7557) which is specific for Mi, but not related proteins (p. 14, lines 25-30). Further, polyclonal antibodies to the same His fusion appear to have been generated and have been shown to not be cross reactive on DNA mobility shift assays (para bridging pages 16-17). Histopathology on human melanoma tissue was performed using antibody D5 to Mi (p. 20, lines 10-15). In addition the specification teaches RT-PCR methods and that RT-PCR and Western blotting were carried out in both murine melanoma and human neuroblastoma cell lines (p. 19, lines 16-24). Using the method, Mi RNA was identified in five melanoma cell lines, but not in two neuroblastoma cell lines (p. 24, lines 18-24).

One cannot extrapolate the teaching of the specification to the scope of the claims because Yasumuto et al (Pigment Cell Research, 1998, 11:329-336) teach that MITF consists of three isoforms, MITF-A, MITF-H, for heart and MITF-M-lineage-specific melanocyte. These isoforms differ in the amino terminal domains but share a transactivation domain and a basic helix-loop-helix and leucine-zipper structure that is required for DNA binding an dimerization. MTF-M is exclusively expressed in melanocytes and melanoma cells but not in other cell types. MITF-A mRNA is widely expressed in many cell types (See the abstract). This finding is reiterated by Shibahara et al (J. Investigative Dermatology Symposium Proceedings, 1999, 4:101-104) who teach that whereas MITF-M mRNA is exclusively expressed in melanocytes and pigmented melanoma cells, MITF-A and MITF-H mRNA are widely expressed in many cell types including retinal pigment epithelium (Abstract). Given that the exemplified assays were all done with probes to the amino acid terminal of MTF-M or the polynucleotide expressing said amino acid terminal, given the art known differences in amino terminal domains of the three isoforms, it cannot be predicted, nor could it be determined whether the assay as broadly claimed could diagnose melanoma by diagnosing a biological specimen with a probe as claimed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would provide guidance to one skilled in the art which would enable one to practice the broadly claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

10. Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 are indefinite because the claim 1 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is contacting a biological specimen of malignant cells. The step is required since there does not appear to be antecedent basis for "a malignant cell" either in the preamble or in step (a). Further, the claims are confusing because although step (b) of the claim requires the assay to be done specifically in a malignant cell, neither the preamble nor step (a) refers to a malignant cell specimen. The rejection may be obviated by amending claim 1, for example to read contacting a biological specimen of malignant cells with a probe.

Claim 3 is indefinite in the recitation of the phrase "wherein the probe the level of mRNA expressing Mi". The claim is confusing because it is not clear what patent protection is being sought.

11. No claims allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
January 17, 2003